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Six-Month Angiographic and Clinical Follow-Up of Patients Prospectively Randomized to Receive Either Tirofiban or Placebo During Angioplasty in the RESTORE Trial

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Objectives. This study sought to investigate the effects of tirofiban versus placebo on the incidence of adverse cardiac outcomes and coronary artery restenosis at 6 months.

Background. Tirofiban is a highly selective, short-acting inhibitor of fibrinogen binding to platelet glycoprotein IIb/IIIa. In a recent clinical study, tirofiban reduced the incidence of adverse cardiovascular events at both 2 and 7 days after coronary angioplasty or directional coronary atherectomy. This reduction persisted but was no longer statistically significant at 30 days.

Methods. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial was a randomized, double-blind, placebo-controlled trial of tirofiban in patients undergoing balloon angioplasty or directional atherectomy within 72 h of presentation with either unstable angina pectoris or acute myocardial infarction. All patients received an initial bolus (10 μg/kg body weight over 3 min), followed by a 36-h infusion (0.15 μg/kg per min) of either tirofiban or placebo.

Results. At 6 months the composite end point (either death from any cause, new myocardial infarction, bypass surgery for angioplasty failure or recurrent ischemia, repeat target vessel angioplasty or stent insertion for actual or threatened abrupt closure) occurred in 1,070 placebo group patients (27.1%) and 1,071 tirofiban group patients (24.1%, $p = 0.11$). Analysis of 6-month coronary arteriograms by means of quantitative coronary arteriography showed no significant difference between placebo- and tirofiban-treated patients in either the incidence of a ≥50% diameter stenosis (57% vs. 51%, p = NS), a loss of ≥50% of lumen diameter gained (50% vs. 50%, p = NS) or a loss of ≥0.72 mm of lumen diameter (44% vs. 42%, p = NS).

Conclusions. The 3% absolute reduction in the incidence of the composite end point at 6 months (27.1% placebo vs. 24.1% tirofiban) was similar to that previously reported at 2 days (8.7% vs. 5.4%, $p < 0.005$), and there does not appear to be any late effect of tirofiban on clinical end points between day 2 and 6 months. Tirofiban did not reduce the incidence of restenosis at 6 months when defined in a number of ways.

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Percutaneous coronary interventions expose many of the highly thrombogenic contents of the arterial wall, and coronary thrombosis remains a persistent problem after conventional balloon angioplasty and directional coronary atherectomy (DCA). Despite standard therapy with aspirin and heparin (1,2), thrombotic occlusion after interventional procedures still occurs in 4% to 12.8% of patients (3–5) and has prompted the search for more effective antiplatelet agents (5–14).

In high risk patients undergoing percutaneous transluminal coronary angioplasty (PTCA), the monoclonal antibody abciximab, directed against the platelet glycoprotein (GP) integrin receptor IIb/IIIa, has been shown to significantly reduce the composite incidence of death, myocardial infarction, emergency repeat angioplasty, emergency coronary artery bypass graft surgery (CABG) or stent implantation by 35% at both 2 and 30 days (5,15–17). Tirofiban (Aggrastat, Merck & Co.) is a synthetic, short-acting, highly selective nonpeptide inhibitor of fibrinogen binding to platelet GP IIb/IIIa (18–22). Potential advantages of this drug include a rapid onset of action, rapid reversal of antiplatelet activity after drug discontinuation, suitability for multiple repeat administrations and high specificity for the GP IIb/IIIa receptor.

The Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) trial (23) was a randomized, double-blind, placebo-controlled trial of tirofiban in patients

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAPTURE = Chimeric c7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (trial)
CTFC = corrected Thrombolysis in Myocardial Infarction (TIMI) frame count
DCA = directional coronary atherectomy
EPILOG = Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GPIIb/IIIa Receptor Blockade
GP = glycoprotein
PTCA = percutaneous transluminal coronary angioplasty
RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis

undergoing PTCA or DCA within 72 h of presentation with either unstable angina pectoris or acute myocardial infarction. Previously, the RESTORE study group has reported (23) that tirofiban compared with placebo reduced the incidence of the composite end point of death, myocardial infarction, any target vessel repeat PTCA or CABG for recurrent ischemia, and stent implantation for abrupt closure by 38% at 2 days ($p < 0.005$) and by 27% at 7 days ($p = 0.022$) largely due to a reduction in nonfatal myocardial infarction and the need for repeat angioplasty. The primary composite end point at 30 days was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group, a 16% relative reduction ($p = 0.16$). When only repeat angioplasty and CABG performed on an urgent (i.e., emergency) basis were included as components of the 30-day composite, the 10.5% event rate in the placebo group was reduced to 8.0% in the tirofiban group, a 24% relative reduction ($p = 0.052$) (23). The incidence of bleeding and thrombocytopenia did not differ significantly between tirofiban- and placebo-treated patients.

The effect of tirofiban and other GP IIb/IIIa inhibitors on angiographic restenosis is unknown. The goal of the 6-month clinical and angiographic substudies was to investigate the effects of tirofiban compared with placebo on the incidence of adverse cardiac outcomes and on coronary artery restenosis as measured by quantitative angiography.

Methods

RESTORE trial. The RESTORE trial (23) was a randomized, double-blind, placebo-controlled trial of tirofiban in aspirin- and heparin-treated patients undergoing PTCA or DCA within 72 h of presentation with acute coronary syndromes (either unstable angina or an acute myocardial infarction). *Unstable angina* was defined as typical anginal pain at rest or with minimal effort and either 1) electrocardiographic changes; 2) hemodynamic changes suggestive of myocardial ischemia; or 3) angiographic evidence of thrombus in the target vessel immediately before PTCA or DCA (characterized by a stenosis >70% with a hazy appearance, intraluminal filling defect, overhanging edge, high degree of eccentricity or reduced Thrombolysis in Myocardial Infarction [TIMI] flow grade). *Acute myocardial infarction* was defined as typical ischemic pain lasting >20 min with ST-T wave changes or pathologic Q waves and a serum creatine kinase elevation greater than twice the upper limit of normal or an elevated creatine kinase-MB fraction value.

Treatment and adjunctive medical therapy. Patients received 300 to 325 mg of aspirin orally within 12 h of PTCA or DCA. Guidelines for heparin administration during PTCA were a maximal initial bolus of 10,000 U before the procedure (weight adjusted to 150 U/kg for patients <70 kg), and intraprocedural heparin was administered as required to maintain an activated clotting time of 300 to 400 s. After the lesion was crossed with the guide wire, the patient was randomized to receive either a bolus of tirofiban (10 μg/kg body weight) or placebo intravenously over 3 min. Each patient then received an intravenous infusion of tirofiban (0.15 μg/kg per min) or placebo for 36 h. Operators were urged to place intracoronary stents only in urgent "bailout" situations (e.g., actual or threatened abrupt closure). The decision to perform DCA or PTCA was left to the discretion of the operator. Investigators were advised to discontinue heparin administration at the conclusion of the PTCA or DCA procedure and to remove sheaths when the activated clotting time was <180 s.

Coronary arteriographic substudy. Selected study sites enrolled all consecutive patients in the angiographic substudy until a total of ~500 patients had been enrolled. At the beginning of the PTCA or DCA procedure, nitroglycerin (200 μg intracoronary) was administered into each coronary artery (left and right coronary arteries) before repeat angiography. At the completion of the procedure, nitroglycerin (200 μg intracoronary) was readministered into each coronary artery (left and right coronary arteries) before repeat angiography. For the 6-month follow-up angiogram, the catheterization laboratory, the equipment used, the procedure followed (including angles and magnifications used) and the therapy given were identical.

For the baseline preprocedural and postprocedural angiograms the angiographically "optimal" view (i.e., without vessel overlapping or foreshortening) and the view orthogonal to it were recorded on cine film at 4- to 5-in. magnification. When two good views were not available, a single view was used that showed the stenosis in its greatest severity without foreshortening, motion blur or overlapping of branches. A portion of the non–contrast-filled catheter shaft was visible during some phase of the injection to allow for calibration and was centered in the image field whenever possible to minimize the impact of diaphragm distortion.

Follow-up angiography was performed as close to 6 months after the index procedure as possible; however, angiography performed between 17 and 30 weeks after the initial PTCA or DCA was accepted. If repeat cardiac catheterization was necessary before the end of 16 weeks, and there was evidence of restenosis, this early angiogram was used as the follow-up angiogram and a repeat 6-month follow-up angiogram was not necessary. However, if there was no evidence of restenosis, angiography was repeated between 17 and 30 weeks. All

follow-up angiography was completed before the end of study week 30. Patients who underwent intracoronary stent placement at the time of the initial procedure were not required to return for coronary arteriography.

Quantitative angiography. All physicians and technicians in the angiographic core laboratory were blinded to treatment group assignment, the investigative center's interpretation of the angiogram and the clinical outcome of the patient. A previously described and validated automated edge detection algorithm was utilized for quantitative angiographic analysis (24). *Restenosis* in the target culprit lesion was prospectively defined as follows: 1) ≥50% diameter stenosis at the time of follow-up angiography in those patients who had a <50% stenosis after the initial intervention; 2) late loss in minimal lumen diameter ≥0.72 mm (25); 3) late loss ≥50% of the initial gain in minimal lumen diameter. *Flow* before and after PTCA was assessed according to both the conventional TIMI flow grade classification scheme (26) and the corrected TIMI frame count (27). *Thrombus grade* was assessed using the standard TIMI definitions (28).

Clinical end points. The clinical end points of the study were death from any cause; new myocardial infarction, CABG for angioplasty failure or recurrent ischemia; repeat target vessel revascularization for recurrent ischemia; implantation of an intracoronary stent because of actual or threatened abrupt closure of the target vessel; and a composite end point, which was the occurrence of any of these events (23). End points were evaluated at 2, 7 and 30 days, and at 6 months. The prespecified primary hypothesis of the study was that tirofiban would result in a reduction in the 30-day composite end point compared with placebo (23). All end points were adjudicated by an independent, blinded end point classification committee according to previously reported definitions (23).

Statistical analysis. The statistical significance of the differences between treatment groups with respect to the composite end point and its components was assessed using logistic regression analysis (PROC LOGISTIC, SAS) (29). The dependent variable was an indicator for whether the patient experienced the specific end point. The analysis was based on the number of patients, not events; any patient experiencing one or more of the composite events within the specific time periods was counted as having a primary event. The independent variables included an indicator of treatment group and the following two covariates: inclusion criteria (unstable angina, acute myocardial infarction within 3 days, acute myocardial infarction treated with primary PTCA) and the primary procedure (DCA or PTCA). The incidence of restenosis was assessed using chi-square analysis. All tests were two-sided, and statistical significance was declared if $p \leq 0.05$. Cumulative event rates over time were plotted using Kaplan-Meier curves.

Results

Patients. The trial included 2,212 randomized patients. The study drug (tirofiban or placebo) was not administered in 71 patients (either because the angioplasty procedure was not performed or the indication for angioplasty changed); therefore, a total of 2,141 patients received study drug infusion and were included in the efficacy and safety analyses as prespecified in the protocol (23). Of these patients, 619 (315 for the placebo group, 314 for the tirofiban group) were enrolled in the 6-month angiographic restenosis substudy. Paired serial angiograms were available for 416 (67.2%) of these 619 patients (205 for the placebo group, 211 for the tirofiban group). Among tirofiban-treated patients, 1,057 (99%) of 1,071 were available for 6 month follow-up, and among placebo patients, 1,050 (98%) of 1,070 were available.

Table 1. Baseline Characteristics of Patients in RESTORE Angiographic Substudy*

	Placebo Group (n = 205)	Tirofiban Group (n = 212)
Mean age (yr)	58.8	59.9
Men	147 (72.4%)	156 (73.6%)
Risk factor		
Diabetes mellitus	47 (22.9%)	43 (20.3%)
Hypertension	116 (56.6%)	117 (55.2%)
Elevated cholesterol	95 (46.3%)	104 (49.1%)
History of smoking	130 (63.4%)	122 (57.5%)
No. of diseased vessels		
1	121 (59.0%)	106 (50.2%)
2	53 (25.9%)	69 (32.7%)
3	23 (11.2%)	32 (15.2%)
Qualifying event		
Unstable angina	138 (67.3%)	141 (66.8%)
Acute MI		
Nonprimary PTCA	63 (30.7%)	65 (30.8%)
Primary PTCA	4 (2.0%)	5 (2.4%)
Initial procedure performed		
PTCA	189 (92.2%)	194 (91.9%)
DCA	16 (7.8%)	17 (8.1%)

*p = NS for all comparisons. Data presented are mean value or number (%) of patients. DCA = directional coronary atherectomy; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis.

Baseline characteristics. The baseline characteristics of all patients included in the RESTORE trial have been previously reported (23) and were similar between patients treated with tirofiban or placebo. For patients in the 6-month angiographic substudy, baseline clinical characteristics again did not differ between the placebo and tirofiban groups (Table 1) and were similar to those of patients in the overall trial. Fifty-nine percent of substudy patients in the placebo group and 50.2% in the tirofiban group had one diseased vessel, 25.9% and 32.7% had two diseased vessels, and 11.2% and 15.2% had three diseased vessels, respectively (p = NS for treatment group difference). Unstable angina pectoris was the most common inclusion criteria in the placebo (67.3%) and tirofiban (66.8%) groups. The intervention was performed during acute myocardial infarction (i.e., as primary angioplasty) in 2.0% of the placebo group and 2.4% of the tirofiban group. The intervention was performed as a nonprimary procedure within 3 days of

Table 2. Six-Month End Points: RESTORE Angiographic Substudy

	Placebo Group (n = 1,069) [no. (%) of pts]	Tirofiban Group (n = 1,070) [no. (%) of pts]	Risk Reduction	p Value
Composite end point	290 (27.1%)	258 (24.1%)	11%	0.11
Death	15 (1.4%)	19 (1.8%)	NA	0.49
MI	81 (7.6%)	67 (6.3%)	17%	0.23
Procedure				
Repeat PTCA	183 (17.1%)	168 (15.7%)	8%	0.36
CABG	73 (6.8%)	59 (5.5%)	9%	0.21
Stent for abrupt closure	27 (2.5%)	16 (1.5%)	40%	0.09

CABG = coronary artery bypass graft surgery; pts = patients; other abbreviations as in Table 1.

Table 3. Initial Angiographic and Procedural Characteristics: RESTORE Angiographic Substudy

	Placebo Group (n = 205)	Tirofiban Group (n = 212)	p Value
Target vessel			
LAD	74 (36%)	86 (41%)	0.37
LCx	44 (21%)	41 (19%)	0.63
RCA	71 (35%)	73 (34%)	0.98
Other	16 (8%)	12 (6%)	0.44
Before procedure			
Ref diam (mm)	2.70 ± 0.57	2.77 ± 0.74	0.27
MLD (mm)	0.54 ± 0.33	0.57 ± 0.39	0.39
% DS (%)	80.5 ± 11.5	79.3 ± 13.3	0.36
After procedure			
Ref diam (mm)	2.66 ± 0.57	2.74 ± 0.72	0.23
MLD (mm)	1.89 ± 0.48	1.89 ± 0.56	0.96
Acute gain (mm)	1.35 ± 0.51	1.32 ± 0.55	0.57
Residual stenosis (%)	28.1 ± 10.4	29.8 ± 12.0	0.15

Data presented are number (%) of patients or mean value ± SD. DS = diameter stenosis; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MLD = minimal lumen diameter; RCA = right coronary artery; Ref diam = reference diameter.

acute myocardial infarction in 30.7% of the placebo group and 30.8% of the tirofiban group. The initial procedure performed was most frequently conventional PTCA (92.2% in the placebo group, 91.9% in the tirofiban group), whereas DCA was performed in the remainder of patients.

Clinical end points. The event rate for the occurrence of the composite end point from the time of randomization through 6 months for all patients is shown in Table 2. At 6 months, the composite end point occurred in 27.1% of placebo-treated patients and 24.1% of tirofiban-treated patients (p = 0.11). These same trends were observed in patients treated both with conventional PTCA (267 [26.8%] of 997 vs. 237 [24.1%] of 985) and those treated with DCA (23 [31.5%] of 73 vs. 21 [24.4%] of 86). The event rates for the individual components of the composite end point are also shown in Table 2. Except for death, all differences in the incidence of end point components were in the same direction, favoring tirofiban, but none was statistically significant. There was a 7.6% rate of acute myocardial infarction in the placebo group versus a 6.3% rate of acute myocardial infarction in the tirofiban group (p = 0.22) and a 1.4% mortality rate in the placebo group versus a 1.8% mortality rate in the tirofiban group (p = 0.49). Tirofiban did not significantly reduce the risk of repeat angioplasty (15.7% for tirofiban vs. 17.1% for placebo, p = 0.38) or CABG procedures (5.5% for tirofiban vs. 6.8% for placebo, p = 0.20).

Angiographic substudy. All baseline (before and after intervention) angiographic lumen dimensions were similar in the two groups (Table 3). The reference diameter for arteries was 2.70 ± 0.57 mm for the placebo group and 2.77 ± 0.74 mm for the tirofiban group. Initial minimal lumen diameter was 0.54 ± 0.33 mm for the placebo group and 0.57 ± 0.39 mm for the tirofiban group. The postprocedural minimum lumen diameter was 1.89 ± 0.48 mm for the placebo group and 1.89 ± 0.56 mm for the tirofiban group.

There was no difference between the placebo and tirofiban groups in either the preinterventional CTFC (47.8 ± 33.0 vs 52.0 ± 34.5, respectively, p = NS) or the TIMI flow grade distribution (41% TIMI grade 3 flow and 19% TIMI grade 0 or 1 flow for placebo vs. 37% TIMI grade 3 flow and 19% TIMI grade 0 or 1 flow for tirofiban, p = NS for both comparisons) (Table 4). After PTCA or DCA there was no significant difference in the CTFC between the two groups (18.2 ± 11.3 for placebo vs. 20.2 ± 12.5 for tirofiban), but there was a difference in the incidence of TIMI grade 3 flow (94% for placebo vs. 85% for tirofiban, p < 0.001). This difference can be accounted for by the greater incidence of TIMI grade 2 fast flow (minimally delayed flow) in the tirofiban group (4% for placebo vs. 14% for tirofiban, p < 0.001) such that when TIMI grade 2 fast flow was combined with TIMI grade 3 flow, there

Table 4. Flow Data: RESTORE Angiographic Substudy

	Placebo Group (n = 205)	Tirofiban Group (n = 212)	p Value
Initial Procedure			
Pretreatment TIMI grade 3 flow	85 (41%)	77 (37%)	0.42
Pretreatment CTFC	47.8 ± 33.0	52.0 ± 34.5	0.25
Posttreatment TIMI grade 3 flow (normal flow)	189 (94%)	178 (85%)	< 0.001
Posttreatment TIMI grade 2 fast flow (minimally delayed flow)	8 (4%)	29 (14%)	< 0.001
Posttreatment TIMI grade 2 fast flow/grade 3 flow (combined)	197 (98%)	207 (99%)	0.41
Posttreatment CTFC	18.2 ± 11.3	20.2 ± 12.5	0.17
Follow-Up Angiography			
6-mo follow-up TIMI grade 3 flow	129 (64%)	129 (62%)	0.69
6-mo follow-up CTFC	37.5 ± 28.5	37.0 ± 26.7	0.87
Change in CTFC			
Pretreatment–posttreatment	28.1 ± 32.0	30.1 ± 34.4	0.62
Follow-up–posttreatment	18.5 ± 30.3	16.1 ± 27.8	0.51
Pretreatment–follow-up	12.0 ± 36.9	14.2 ± 35.4	0.6

Data presented are mean value ± SD or number (%) of patients. CTFC = corrected Thrombolysis in Myocardial Infarction (TIMI) frame count.

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Table 5. Six-Month Follow-Up: RESTORE Angiographic Substudy

	Placebo Group (n = 205)	Tirofiban Group (n = 212)	p Value
MLD (mm)	1.19 ± 0.68	1.22 ± 0.71	0.62
≥50% loss of gain	102 (50%)	105 (50%)	0.96
% DS ≥50%*	110 (57%)	100 (51%)	0.2
Loss ≥0.72 (mm)	90 (44%)	88 (42%)	0.69
Late loss (mm)	0.70 ± 0.73	0.67 ± 0.72	0.67
Loss index	0.51 ± 0.58	0.50 ± 0.57	0.88

*Requires initial post–coronary angioplasty stenosis <50% (193 for placebo, 196 for tirofiban). Data presented are mean value ± SD or number (%) of patients. Abbreviations as in Table 3.

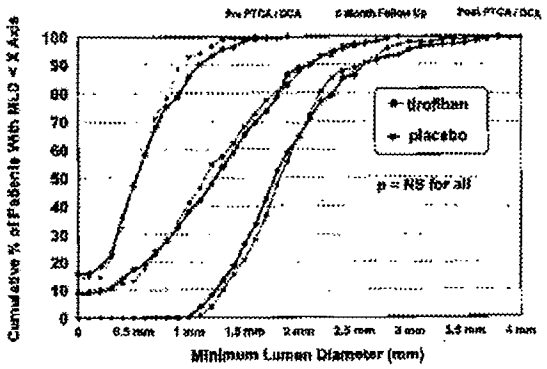

Figure 1. Cumulative distribution functions of minimal lumen diameters before and after intervention and at 6 months of follow-up for tirofiban- and placebo-treated patients. As can be seen, the cumulative distribution functions do not differ significantly between the treatment groups and are nearly superimposible at all time points.

was no significant difference between the two groups (98% for placebo vs. 99% for tirofiban, p = NS). There were no significant differences between groups in TIMI grade 0 or 1 flow (0.5% for placebo vs. 0.0% for tirofiban, p = NS) or TIMI grade 2 slow flow (markedly delayed flow) (2% vs. 1%, respectively, p = NS). Moreover, there was no difference in the change in CTFC from before to after angioplasty between the two groups (28.1 ± 32.0 for placebo vs. 30.1 ± 34.4 for tirofiban, p = NS).

There was no difference between the tirofiban and placebo groups when 6-month restenosis was defined in a number of ways (Table 5). A ≥50% loss of lumen diameter gained after the initial procedure occurred in 50% of both the placebo and tirofiban groups (p = 0.99). A ≥50% stenosis at the time of follow-up angiography was present in 57% (n = 193) of the arteries in the placebo group and in 51% (n = 196, p = 0.26) of those in the tirofiban group (only arteries with <50% stenosis at the initial postprocedural angiographic analysis were included in this analysis). A minimal lumen diameter loss ≥0.72 mm was present in 44% of arteries in the placebo group and in 42% of those in the tirofiban group (p = 0.69). The late loss for tirofiban-treated patients did not differ from that of placebo-treated patients (0.67 ± 0.72 mm vs. 0.70 ± 0.73 mm, p = NS), and likewise, the loss index (late loss divided by acute gain) for tirofiban-treated patients did not differ from that of placebo-treated patients (0.50 ± 0.57 vs. 0.51 ± 0.58, p = NS). Figure 1 shows virtually superimposable cumulative distribution functions for the minimum lumen diameters before and after PTCA and at follow-up. Patients with angiographic thrombus (TIMI flow grades 2 to 4) (28) were not found to have a higher risk of restenosis than patients without angiographically apparent thrombus (54% vs. 56%, respectively, p = NS).

Discussion

Acute coronary artery occlusion and delayed restenosis remain major limitations of percutaneous coronary revascularization. Recently, the RESTORE study group reported (23) that a 36-h infusion of tirofiban reduced the relative incidence of the prespecified composite end point of adverse cardiac outcomes by 38% (3.3% absolute reduction) at 2 days (p < 0.005), and by 27% at 7 days (2.3% absolute reduction) (p = 0.02). However, by 30 days the relative risk reduction decreased to 16% (1.9% absolute reduction) and was not statistically significant (23). Although the 3% absolute reduction in the incidence of the composite end point at 6 months (27.1% placebo vs. 24.1% tirofiban) was similar to that previously reported at 2 days (8.7% vs. 5.4%, p < 0.005), this 11% relative reduction in the composite end point did not reach statistical significance (p = 0.11). These benefits were obtained without a significant increase in thrombocytopenia or major bleeding complications in the tirofiban group versus the placebo-treated group (23).

It could be hypothesized that residual thrombus at the completion of an intervention may form a nidus for cellular organization and may contribute in part to the risk of restenosis. However, in the present study patients with angiographically apparent thrombus were not found to have a higher risk of restenosis than patients without thrombus (54% vs. 56%). There was also no difference in clinical restenosis between the tirofiban and placebo groups. The 3% absolute reduction in the composite end point was achieved early and was already apparent at 2 days. The cumulative event curves remained relatively parallel beyond this time point out to 6 months (Fig. 2). Moreover, in the present, and to our knowledge the first, angiographic substudy to be reported for a GP IIb/IIIa inhibitor, we found that tirofiban did not reduce the incidence of angiographic restenosis when defined in a number of ways. There was no significant difference in the number of arteries with ≥50% stenosis, ≥50% loss of lumen diameter gained or ≥0.72-mm loss of lumen diameter between the two groups. Likewise, there was no difference in either the late loss or the loss index between the tirofiban and placebo groups. Indeed, Figure 2 shows virtually superimposable cumulative distribution functions for the minimum lumen diameters before and after PTCA and at follow-up.

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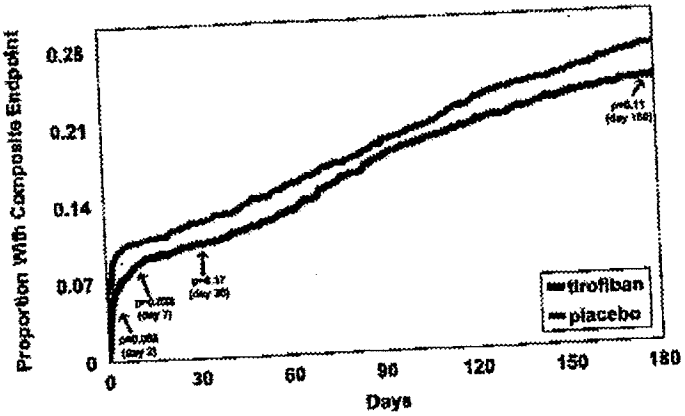

Figure 2. Kaplan-Meier curves of clinical outcomes at multiple time points. The 3% absolute reduction in this composite end point that was observed within 48 h of initial treatment persisted over the 6-month follow-up period, but there was no evidence of additional late clinical benefit. At 6 months, the composite end point occurred in 1,069 placebo-treated patients (27.1%) and in 1,078 tirofiban-treated patients (24.1%, p = 0.11).

Previous reports. Previous reports have suggested (15) that abciximab, an antibody with a longer duration of action and other potential non GP IIb/IIIa receptor blocking activities, may reduce the incidence of clinical restenosis. The Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial (15) of abciximab in high risk patients undergoing angioplasty reported a 26% decrease in repeat target vessel revascularization at 6 months. An angiographic substudy was not performed in that trial to assess restenosis rates. This effect of abciximab was not reproduced in two subsequent trials of angioplasty in patients with refractory unstable angina (Chimeric c7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment [CAPTURE] trial [30]) at lower risk (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GPIIb/IIIa Receptor Blockade [EPILOG] trial [31]). In the CAPTURE trial, when abciximab was infused predominantly before PTCA, there was no difference in death, myocardial infarction or repeat revascularization at 6 months between abciximab- and placebo-treated patients. In the EPILOG trial, a 3% absolute difference was evident in this composite end point between abciximab- and placebo-treated patients, similar to that observed in the RESTORE trial. There was no difference in the rates of repeat revascularization. No angiographic follow-up data have yet been reported from the EPILOG trial. In the only other large-scale trial of GPIIb/IIIa inhibitor in PTCA, the Integrelin to Manage Platelet Aggregation to Combat Thrombosis (IMPACT) II trial of Integrilin (eptifibatide) (32), the absolute reduction in composite end point seen at 30 days (2.2%, low dose eptifibatide vs. placebo) persisted at 6 months but was not statistically significant.

Study limitation. The main limitation of this study was the relatively low rate of follow-up angiography (67%) in the angiographic substudy. That the substudy cohort was enriched with symptomatic patients may account, in part, for the relatively high rates of restenosis that were observed. Nonetheless, the angiographic substudy cohort was representative of the overall study group, and there was no difference in follow-up rates between the two treatment groups. Thus, the low rate of angiographic follow-up is unlikely to have been a source of treatment bias.

Conclusions. Six-month follow-up of patients undergoing high risk PTCA or DCA in the RESTORE trial demonstrated no significant benefit of tirofiban in reducing the composite clinical end point of death, myocardial infarction, CABG or repeat PTCA of the target vessel. The 3% absolute reduction in this composite end point that was observed within 48 h of initial treatment persisted over the 6-month follow-up period, but there was no evidence of additional late clinical benefit. Angiographic follow-up of a subset of patients demonstrated that tirofiban did not reduce angiographic restenosis.

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Usefulness of Subcutaneous Low Molecular Weight Heparin (*Ardeparin*) for Reduction of Restenosis After Percutaneous Transluminal Coronary Angioplasty

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In addition to its anticoagulant effects, heparin is known to have antiproliferative effects on vascular smooth muscle cells. Ardeparin is a partially depolymerized (low molecular weight) heparin that has a longer half-life than unfractionated heparin. Following successful coronary balloon angioplasty, 565 patients were randomized to treatment with twice-daily subcutaneous ardeparin 50 anti-Xa U/kg (low dose) or 100 anti Xa U/kg body weight (high dose), or placebo for 3 months. Follow-up angiography was performed in 415 patients at 4 months, or earlier if clinically indicated. Additionally, patients underwent treadmill exercise electrocardiography at 2 weeks and 4 months. This study was designed to test the hypothesis that 3 months of subcutaneous dosing of ardeparin would reduce angiographic restenosis after coronary balloon angioplasty. Ardeparin had no effect on the incidence of angiographic restenosis (prespecified definition: ≥50% luminal diameter narrowing plus a loss of 50% of initial gain or absolute decrease of 20% of luminal diameter). Neither the mean luminal diameters nor mean percent diameter stenoses were different among the treatment groups before, after, or 4 months after balloon angioplasty. On exercise electrocardiography at 2 weeks and 4 months, patients in all treatment groups had similar exercise tolerance, incidence of angina, and frequency of ST depression. Thus, ardeparin treatment given subcutaneously for 3 months after successful balloon angioplasty does not reduce either angiographic or clinical measures of restenosis. ©1999 by Excerpta Medica, Inc.

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Heparin is known to have both anticoagulant and antiproliferative effects.[1,2] Both anticoagulant and nonanticoagulant heparin fragments have been developed that inhibit the proliferation of vascular smooth muscle cells in vivo and in vitro.[3] Thrombin[4] and factor Xa have been demonstrated to be potent mitogens for vascular smooth muscle cells in culture. Ardeparin is a low molecular weight heparin that acts through the same mechanisms as heparin, but with different pharmacokinetics. Ardeparin is over 90% bioavailable after subcutaneous administration, as measured by plasma anti-Xa activity.[5] Its half-life, 2.5 to 3.3 hours by anti-Xa assay, is longer than that of heparin.[6] Ardeparin binds less to nonanticoagulant plasma proteins, resulting in more predictable plasma drug levels. These kinetics might be more appropriate for extended therapy, if shown to be safe and effective. Ardeparin and other low molecular heparins have been shown to be safe and effective in certain clinical subsets for prevention of deep venous thrombosis, and these agents are being actively studied in various coronary syndromes,[7] including restenosis.[8–11] We hypothesized that low molecular weight heparin, given within 12 hours after successful balloon angioplasty and continued by subcutaneous administration for 3 months, would decrease angiographic restenosis at 4 months.

METHODS

Study design: This was a randomized, multicenter, double-blind, placebo-controlled, stratified, and parallel study. Only patients undergoing successful balloon angioplasty were enrolled; patients with stents were not included.

Inclusion criteria: Patients >25 years of age undergoing percutaneous transluminal coronary angioplasty (PTCA) of 1 or 2 lesions (≥50% stenosis) were eligible. PTCA must have been successful in the opinion of the investigator at the clinically most significant lesion. Patients must have presented initially with symptomatic coronary artery disease and/or laboratory evidence of spontaneous or inducible myocardial ischemia. The protocol was approved at each institution by the appropriate human research committee and written informed consent was obtained from all patients.

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Exclusion criteria: Patients with lesions located at previous PTCA sites, in vascular grafts, or in any part of a native vessel supplied by a patent graft were excluded. Patients were excluded for any condition that might be adversely affected by participation, including conditions that would require a major surgical procedure before 3 months after PTCA. Additionally, patients were excluded for any of the following reasons: >100 kg body weight, underlying bleeding disorder, a history of internal bleeding or intraocular surgery, any history of transient ischemia attack, stroke, intracranial bleeding or other intracranial vascular malformation/aneurysm, treatment with thrombolytic therapy or oral anticoagulants in the 5 days before PTCA, inability or unwillingness to self-administer subcutaneous injections, active alcohol or drug abuse, known hypersensitivity to heparin, pork products, or aspirin, cardiopulmonary resuscitation in the 2 weeks before PTCA, platelet count $<100 \times 10^9$/L, systolic pressure >200 or diastolic >100 mm Hg, patients requiring chronic aspirin administration (>81 mg), previous PTCA on the same coronary lesion or any PTCA in the previous 6 months, or myocardial infarction in the 5 days before PTCA. Women of childbearing potential were also excluded.

Drug administration Ardeparin is a low molecular weight heparin that is made from porcine mucosal heparin by peroxidative depolymerization. Ardeparin has the same molecular subunits as standard heparin but has shorter molecular chain lengths. The mean molecular weight of ardeparin is 6,000 ± 350 daltons (range of 2,000 to 15,000). The specific activities of ardeparin are 120 ± 25 anti-Xa U/mg and 60 ± 15 anti-IIa U/mg. For this study, 2 formulations of ardeparin were used, namely 10,000 and 20,000 anti-Xa U/ml, to preserve the double-blind nature of the treatments.

Study drug administration began within 12 hours of the discontinuation of unfractionated heparin or administration of the last unfractionated heparin bolus. Patients were randomized (after the PTCA procedure) to receive subcutaneous injections of either ardeparin 50 anti-Xa U/Kg (low dose) or 100 anti-Xa U/Kg body weight (high dose), or placebo twice daily for 3 months. Before discharge, each patient received instructions regarding self-administration of subcutaneous injections.

Concomitant treatment: Aspirin (81 mg/day) was administered before PTCA and during follow-up. Use of other anticoagulant drugs (other than study drug), fibrinolytic drugs, pharmacologic doses of fish oils, or other aspirin-containing drugs was not permitted during the 4-month follow-up period.

Quantitative coronary angiography: Intracoronary nitroglycerin (200 μg left coronary artery, 100 to 200 μg right coronary artery) was given, and angiographic images were obtained before and after angioplasty and again at 4 months using identical camera angulation at each time point. Angiographic restenosis was assessed at a core facility by computer-assisted quantitative coronary angiography using the PIE Medical CAAS system (Maastricht, The Netherlands). The angiographic core laboratory procedure involved: (1) initial review of film for image quality; (2) optical magnification and digitization of selected images of study lesion and scaling catheter; (3) computer detection of vessel and catheter edges; (4) manual correction of computer-derived edges (if necessary); (5) computer identification of reference segment; (6) manual correction of reference segment selection (if necessary); (7) review of analysis results by core laboratory staff; and (8) generation of analysis report. Percent diameter stenosis, minimal luminal diameter, lesion length, and reference diameters were reported for each lesion dilated. For the primary end point, the "primary lesion" for each patient was identified by the principal investigator at each clinical site at the time of angioplasty.

TABLE 1 Flow Chart of Patients Undergoing Protocol Angiography

	Placebo	Low Dose	High Dose
Randomized	187	191	187
Withdrawals from angioplasty			
Adverse reaction	2	2	11
Other medical event	11	6	9
Other nonmedical event	2	4	4
Patient request	13	20	23
Protocol violation	4	4	6
Angiography not in 90- to 150-day window	10	8	11
Total analyzed for the angiographic end points	145	147	123

Primary end points: The primary efficacy end point (at 3 to 5 months after PTCA) was the reduction in the incidence of angiographic restenosis with respect to the primary lesion. Restenosis was prospectively defined as a ≥50% luminal diameter narrowing plus at least 1 of the following criteria: either a loss of 50% of the initial gain achieved at PTCA or the absolute decrease of at least 20% of the total luminal diameter at the time of 4-month angiography. A secondary angiographic definition of restenosis was the loss of ≥0.72 mm in minimal luminal diameter between the immediate and 4-month post-PTCA angiograms. Data were also analyzed as cumulative probabilities in each treatment group based on minimal luminal diameters and percent diameter stenosis by angiography.

Bleeding complications: Bleeding complications were categorized at each clinical site as mild, moderate, or severe. In addition, the number of patients discontinuing participation in the study because of bleeding was assessed in each group. Hematocrit was followed at 1, 2, 4, 8, 16, and 36 weeks after randomization.

Anti-Xa assays: Anti-Xa levels drawn 6 hours after study drug dosing were measured by a core laboratory. Following clean venipuncture, blood (4.5 ml) was drawn into a citrated siliconized tube, centrifuged immediately at high speed, and plasma was stored at −20°C or colder. Plasma anti-Xa activity was determined using a chromogenic substrate assay as previously described.[12]

Statistical analysis: To show a statistically significant decrease in the restenosis incidence from 35% (expected rate for placebo) to 20% in 1 of the ardeparin treatment groups (90% power, $\alpha = 0.05$), a

TABLE II Demographic Comparisons* in Angiographic Cohort

Treatment Group	Placebo (n = 145)	Low-Dose Ardeparin (n = 147)	High-Dose Ardeparin (n = 123)
Age (yr)	59 ± 11	58 ± 20	56 ± 10
Male (%)	74	82	77
Weight (kg)	81 ± 12	81 ± 12	82 ± 13
Prior tobacco use (n)	108	103	84
Tobacco use at follow-up (n)	28	29	26
Total cholesterol (mg/dl)	209 ± 42	207 ± 44	206 ± 35
HDL (mg/dl)	38 ± 13	38 ± 15	39 ± 12
Triglyceride (mg/dl)	194 ± 126	216 ± 179	191 ± 113
Any prior MI (n)	72	78	62
MI during month before PTCA (n)	34	32	34
LAD as PTCA vessel (n, %)	56 (39%)	58 (39%)	48 (39%)
Hypertension (n)	72	75	62
Ejection fraction (%)	58 ± 14	56 ± 12	57 ± 13

*None of the demographic comparisons was significantly different.
HDL = high-density lipoprotein; LAD = left anterior descending coronary artery; MI = myocardial infarction.

TABLE III Ardeparin Administration Data in Angiographic Cohort

Treatment Group	Placebo (n = 145)	Low-Dose Ardeparin (n = 147)	High-Dose Ardeparin (n = 123)	p Value
Time on Rx (d)	86.3 ± 14.3	84.1 ± 18.4	84.4 ± 16.9	NS
Stopped Rx within 60 days (n)	4	9	7	NS
Anti-Xa levels (U/ml)				
Week 1	0.05 ± 0.09	0.13 ± 0.01	0.32 ± 0.16	<0.001
Week 2	0.05 ± 0.04	0.22 ± 0.11	0.48 ± 0.24	<0.001
Week 4	0.04 ± 0.03	0.24 ± 0.10	0.58 ± 0.23	<0.001
Week 8	0.06 ± 0.05	0.23 ± 0.11	0.56 ± 0.27	<0.001
Week 16	0.05 ± 0.04	0.07 ± 0.04	0.07 ± 0.04	NS

Rx = therapy.

sample size of 197 patients per group was anticipated. Based on power calculations, it was anticipated that approximately 675 patients would be enrolled to provide for the completion of 600 available patients at approximately 10 to 15 centers. Dropouts for reasons other than safety or lack of efficacy were anticipated to be replaced. An interim efficacy analysis was planned after approximately 300 patients had undergone follow-up angiography.

Categorical data were compared using chi-square analysis. Data are expressed as mean value ± SD. Continuous variables were compared among treatment groups using 1-way analysis of variance. A p value <0.05 was considered significant.

RESULTS

Five hundred sixty-five patients undergoing successful balloon angioplasty were randomized in this trial. Of these, 415 were included in the analysis of angiographic restenosis (analysis included patients with angiographically confirmed early restenosis and those undergoing protocol follow-up angiography between 90 and 150 days). The reasons for failure to undergo follow-up angiography are shown in Table I. There were no significant demographic or angiographic differences between patients who did and did not undergo follow-up angiography. There was no significant difference between the ardeparin treatment groups or placebo with respect to the number of patients failing to undergo follow-up angiography. Exercise electrocardiography was performed in 404 patients at 2 weeks. Repeat exercise electrocardiography was performed in 287 patients without clinical restenosis at 4 months. The trial was terminated early when a prospectively planned, interim analysis produced 2 estimates of conditional power: one for the comparison of low-dose ardeparin versus placebo and the other for high-dose ardeparin versus placebo. For both comparisons, conditional power was estimated to be <25% if the trial were to be continued to its planned recruitment of 200 patients per group.

Among the patients in the angiographic cohort, the mean time on therapy for patients not experiencing clinical restenosis was 85 ± 15 days, and only 4.5% of patients failed to complete at least 60 days of therapy. Patient demographic data and treatment group assignment are shown in Table II. Most of the patients were men, and many patients had a prior history of smoking. Prior infarction had occurred in 212 of 415 patients (51%), but mean ejection fraction at the time of angioplasty was 58 ± 13%.

Hematocrit, platelet counts, and anti-Xa levels: Serum hematocrit, hemoglobin levels, and platelet counts were measured at baseline and after 1, 2, 4, 8, 16, and 36 weeks of randomization. No significant differences with respect to these parameters were observed among the treatment groups at these time points. Anti-Xa levels from plasma samples collected during the follow-up period are shown for the angiographic cohort in Table III. As expected, there were significant graded differences among the treatment groups and placebo with respect to anti-Xa levels. There were no correlations observed, however, between angiographic outcomes, restenosis, or clinical outcomes with respect to the anti-Xa levels.

Complications of ardeparin: Bleeding is the primary concern with anticoagulant therapies. Severe bleeding events were observed in 7 patients, namely 1 in the ardeparin low-dose group and 6 in the ardeparin high-dose group (none in the placebo group). All these events were hematomas, often occurring at the sites of catheterization or subcutaneous injections. Two of these 7 patients, both of whom were in the ardeparin high-dose group, were withdrawn from the study because of the events. Twelve patients discontinued the protocol because of bleeding. Nine of these were in the high-dose ardeparin group, 2 in the low-dose group, and 1 in the placebo group.

TABLE IV Angiographic Comparisons*

Treatment Group	Placebo (n = 145)	Low-Dose Ardeparin (n = 147)	High-Dose Ardeparin (n = 123)
Days to follow-up angiography	118 ± 25	118 ± 35	113 ± 42
Restenosis			
Primary binary definition (n[%])	61 (42.1%)	61 (41.5%)	61 (49.6%)
Secondary binary definition (n[%])	49 (33.8%)	44 (30.0%)	41 (33.3%)
Luminal diameter before PTCA (mm)	0.89 ± 0.36	0.91 ± 0.38	0.88 ± 0.43
Percent diameter stenosis before PTCA	68.12 ± 11.78	69.23 ± 11.57	69.85 ± 13.77
Luminal diameter after PTCA (mm)	1.93 ± 0.37	1.90 ± 0.42	1.92 ± 0.40
Percent diameter stenosis after PTCA	32.88 ± 9.17	35.63 ± 10.28	34.07 ± 10.25
Luminal diameter 4 mos (mm)	1.42 ± 0.55	1.47 ± 0.61	1.36 ± 0.58
Percent diameter stenosis 4 mos	48.34 ± 17.80	49.10 ± 18.90	52.00 ± 19.75
Lesion length before PTCA	7.39 ± 2.45	8.02 ± 3.03	7.95 ± 3.25
Lesion length 4 mos	6.92 ± 2.57	7.07 ± 3.25	7.51 ± 3.30
Initial gain (mm) before to after PTCA	1.03 ± 0.47	0.99 ± 0.43	1.05 ± 0.46
Late loss (mm) after to 4 mos after PTCA	−0.50 ± 0.55	−0.44 ± 0.54	−0.56 ± 0.57
Reference diameter			
Before PTCA (mm)	2.83 ± 0.54	2.96 ± 0.60	2.93 ± 0.52
After PTCA (mm)	2.89 ± 0.54	2.99 ± 0.62	2.93 ± 0.49
4 mos (mm)	2.77 ± 0.53	2.87 ± 0.55	2.85 ± 0.50

*None of the angiographic comparisons was statistically significant.

Primary binary definition of restenosis: ≥50% luminal diameter narrowing plus at least one of the following: either a loss of 50% of the initial gain or the absolute decrease of at least 20% of the total minimal diameter at 4 months.

Secondary binary definition of restenosis: loss of ≥0.72 mm in minimal luminal diameter between the immediate post-PTCA and 4-month post-PTCA angiograms.

Angiographic outcomes: Table IV contains the angiographic outcomes at each time point for the 3 treatment groups. For the entire angiographic group, the mean luminal diameter increased from 0.89 ± 0.39 mm before to 1.92 ± 0.40 mm after angioplasty but decreased to 1.42 ± 0.58 mm at 4-month follow-up. There were no significant differences among treatment groups before, after, or 4 months after angioplasty with respect to luminal diameter at the angioplasty site (Table IV and Figure 1). Similarly, the mean percent stenosis at the angioplasty site for the entire angiographic group decreased from 69.0 ± 12.3% before to 34.2 ± 9.9% after angioplasty, but increased to 49.7 ± 18.8% at 4-month follow-up. There were no significant differences among treatment groups before, after, or 4 months after angioplasty with respect to percent stenosis at the angioplasty site. Data were analyzed with respect to other angiographic parameters (outlined in Table IV). There were no significant differences among the groups with respect to lesion length, reference vessel segment diameter, initial angiographic gain (before to after angioplasty), or late loss (after angioplasty to 4-month follow-up).

Analysis of restenosis—primary end points: Angiographic restenosis occurred in 183 patients based on the prospectively defined (binary) definition. Restenosis was equally distributed among the placebo, low-dose ardeparin, and high-dose ardeparin treatment groups, respectively (42.1%, 41.5%, 49.6%, p = NS). Similarly, restenosis based on the second prospectively defined (binary) definition was equally distributed among the 3 treatment groups, respectively (33.8%, 30.0%, 33.3%, p = NS).

Figure 1 demonstrates the cumulative distribution of angiographic parameters in the 3 treatment groups. In panel A, the value on the ordinate represents the cumulative percentage of patients with luminal diameters at the angioplasty site, which was less than or equal to the corresponding value on the abscissa. A horizontal line drawn at 50% would correspond to the median luminal diameter for each patient group. In panel B, the value on the ordinate represents the cumulative percentage of patients with percent diameter stenosis at the angioplasty site, which was less than or equal to the corresponding value on the abscissa. There were no differences in the distributions of angiographic outcomes among the 3 treatment groups either before, after, or 4 months after angioplasty (Figure 1).

Outcomes of treadmill exercise testing at 2 weeks after angioplasty: Among the 404 patients undergoing exercise treadmill testing at 2 weeks (10 to 30 days) after angioplasty, the mean exercise duration was 8.3 ± 3.0 minutes. There were no differences among treatment groups with respect to exercise duration. Angina occurred in 54 of 404 patients (13%) at 2 weeks. ST depression of >1.0 mm occurred in 82 of 404 patients (20%). The exercise electrocardiogram was positive by either the development of angina or ST depression >1.0 mm in 124 of 404 patients (31%). There were no differences observed among treatment groups with respect to any of these exercise variables at 2 weeks (Table V).

Outcomes of treadmill exercise testing at 4 months after angioplasty: Ninety-six patients who developed both clinical and angiographic evidence for restenosis did not undergo exercise testing at 4 months after angioplasty. These were evenly distributed among the treatment groups. Among the remaining patients, 287 of 308 (93%) underwent symptom-limited exercise testing at 4 months. Among these, 32 of 287 (11%) developed angina during exercise, 55 of 287 (19%) had ST depression >1.0 mm, and 65 of 287 (23%) had a positive test with either angina or ST depression. The mean exercise duration was 8.75 ± 2.9 minutes. There were no differences observed among the 3 treatment groups with respect to any of these exercise variables at 4 months (Table V).

DISCUSSION

Multiple in vitro and in vivo studies have suggested that interactions involving thrombosis, coagulation proteins, and the arterial wall may be important in neointimal growth and restenosis. In particular, thrombin and factor Xa have been implicated in many of the processes contributing to restenosis. We had therefore hypothesized that prolonged inhibition of factors Xa and thrombin with low molecular weight heparin would improve clinical outcomes and angiographic parameters in patients after coronary balloon angioplasty. This trial did

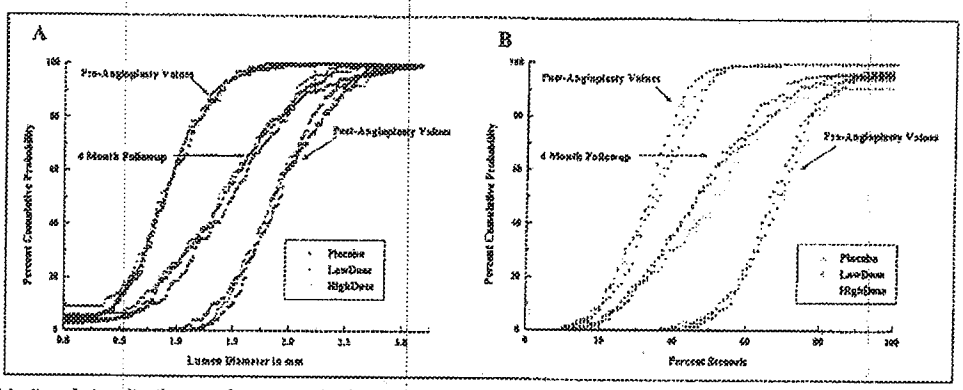

FIGURE 1. *Cumulative distribution of angiographic luminal diameters (panel A) and percent diameter stenoses (panel B) in the 415 patients undergoing angiography before, after, and 4 months after coronary balloon angioplasty. The 3 treatment groups are shown as squares (placebo), circles (low-dose ardeparin), or triangles (high-dose ardeparin). The value on the ordinate represents the cumulative percentage of patients with luminal diameters or percent diameter stenoses less than or equal to the corresponding value on the abscissa. The plot illustrates that the distribution of these angiographic parameters was the same in the 3 treatment groups.*

TABLE V Treadmill Exercise Testing Data at Two Weeks and Four Months

Treatment Group	Placebo (n = 145)	Low-Dose Ardeparin (n = 147)	High-Dose Ardeparin (n = 123)
Two-week data			
Number with exercise test between 10 and 30 days	140	147	117
Angina during test (n)	18	18	18
ST depression >1.0 mm (n)	30	29	23
Angina or ST depression (n)	45	45	34
Exercise duration	8.2 ± 3.0	8.3 ± 3.0	8.3 ± 3.1
Four-month data			
Number with clinical restenosis before to 4-month exercise test	36	27	33
Number with restenosis and exercise test between 90 and 180 days	98	109	80
Angina during test (n)	13	13	6
ST depression >1.0 mm (n)	17	23	15
Angina or ST depression (n)	21	28	16
Exercise duration	9.0 ± 3.0	8.6 ± 2.7	8.7 ± 3.0

None of the exercise testing comparisons was statistically significant.

not, however, demonstrate improvements in patients treated with the 2 doses of ardeparin compared with placebo. We observed no differences with respect to angiographic indexes of restenosis or luminal dimensions. This trial is consistent with previously published reports using unfractionated heparin or other low molecular weight heparins for prolonged periods after angioplasty. These include intravenous unfractionated heparin for 24 hours,[13] unfractionated heparin (12,500 IU subcutaneously twice daily for 4 months),[14] enoxaparin (4,000 anti-Xa U/day for 28 days),[11] enoxaparin (6,000 anti-Xa U/day for 6 weeks) in combination with ω-3 fatty acids,[9] reviparin (7,000 anti-Xa U/day for 28 days) in the Reduction of Restenosis after PTCA (REDUCE) trial,[10] and nadroparin (6,150 anti-Xa U/day for 90 days) in the Fraxiparine Angioplastie Coronaire Transluminale (FACT) study[15] (begun 3 days before angioplasty). The current study using ardeparin used the highest doses of low molecular weight heparin studied to date, with the average patient (81 kg) in the high-dose group receiving 16,200 anti-Xa U/day for 90 days.

There are numerous potential explanations for these negative studies of heparin following balloon angioplasty. It is uncertain that the heparins actually do limit neointimal hyperplasia after balloon injury in humans with complex coronary artery disease. It is possible that bleeding concerns have limited optimal dosing and that logistic issues have limited the duration of heparin pretreatment. Only in the FACT study was pretreatment (for 3 days) with low molecular weight heparin used.[15] The current study, while not using pretreatment, did use the highest doses of low molecular weight heparin (as measured by anti-Xa activity) that have been published. To date, there have been no pharmacologic interventions that have consistently shown reduction in restenosis based on angiographic parameters. The Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) investigators[16] did suggest that fewer revascularization procedures were required in a group of patients treated with c7E3 bolus plus infusion than in those given placebo, but routine angiography was not performed in these patients at follow-up and these results have not been reproduced with other platelet fibrinogen receptor-blocking agents.

The importance of cellular proliferation and intimal hyperplasia in the restenosis process remains poorly defined. Arterial renarrowing after coronary intervention results from complex interactions including arterial recoil, arterial remodeling, and neointimal growth. The relative contribution of these factors may vary among devices and within patient subgroups. Several investigators have emphasized the importance of elastic recoil and

arterial remodeling in the restenosis process.[17,18] Cellular proliferation and neointimal growth therefore may only play a minor contributory role in the restenosis process in many patients. In contrast, coronary stenting minimizes elastic arterial recoil and has been shown to improve clinical outcomes compared with balloon angioplasty. Both the Belgium Netherlands STENT (Benestent) study[19] and the Stent Restenosis[20] studies did show improved angiographic dimensions at 6-month follow-up. Preliminary data suggest that radiation therapy may be useful in limiting neointimal growth after coronary stenting.[21] It remains uncertain whether radiation or other therapies that reduce neointimal growth will reduce angiographic restenosis rates in patients undergoing coronary balloon angioplasty.

Study limitations: Based on the initial power calculation, it was anticipated that 675 patients would be enrolled. The prospectively planned interim analysis, however, determined that the conditional power was <25% for comparison of either dose of ardeparin with placebo. It is therefore unlikely that recruiting more patients would have altered the results. Because the trial was designed to investigate angiographic definitions of restenosis, it was anticipated that a subgroup of patients would "drop out" of the study before 4-month follow-up angiography. The final angiographic cohort, however, was not statistically different from the randomized group. We did not fully classify patients with respect to other clinically defined end points such as "target vessel revascularization," and we are thus unable to report these end points. The exercise variables, however, do not suggest important differences between the randomized patient groups with respect to important exercise-defined outcomes. Our data are thus consistent with the previously reported trials of low molecular weight heparins after coronary balloon angioplasty.

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APPENDIX

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High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization: One-year results from the SCORE randomized trial

Eberhard Grube, Alexandra Lansky, Karl Eugen Hauptmann, Carlo Di Mario, Germano Di Sciascio, Antonio Colombo, Sigmund Silber, Juergen Stumpf, Nicolaus Reifart, Jean Fajadet, Antonio Marzocchi, Joachim Schofer, Pierre Dumas, Rainer Hoffmann, Giulio Guagliumi, Mark Pitney, and Mary E. Russell

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High-Dose 7-Hexanoyltaxol-Eluting Stent With Polymer Sleeves for Coronary Revascularization

One-Year Results From the SCORE Randomized Trial

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OBJECTIVES The Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial was a multicenter, randomized, open-label trial comparing the safety and performance of 13- and 17-mm QuaDDS stents (n = 126) (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) versus uncoated control stents (n = 140) in focal, de novo coronary lesions.

BACKGROUND The pioneering drug-delivery QuaDDS stent used four to six acrylate polymer sleeves, each loaded with 800 μg of the paclitaxel derivative 7-hexanoyltaxol.

METHODS Clinical end points were assessed at 1, 6, and 12 months post procedure. Quantitative coronary angiography and intravascular ultrasound were performed post procedure and at six-month follow-up.

RESULTS In the QuaDDS group, early stent thrombosis and myocardial infarction (MI) rates were significantly higher, leading to premature cessation of enrollment. For the QuaDDS group, the stent thrombosis rate increased from 3.2% to 10.3% between 1 and 12 months, associated with increased non–Q-wave MI and death rates. The angiographic restenosis rate at six months was reduced from 32.7% (control) to 7.4% ($p < 0.0001$). However, the primary end point was not met with six-month target vessel revascularization (TVR) rate as well as the composite major adverse cardiac event rates (cardiac death, MI, and TVR) comparable between groups.

CONCLUSIONS Despite angiographic indications of potential anti-restenotic benefit, increased rates of stent thrombosis, MI, and cardiac death associated with the QuaDDS stent show an unacceptable safety profile. (J Am Coll Cardiol 2004;44:1368–72) © 2004 by the American College of Cardiology Foundation

The use of bare metal coronary stents after balloon angioplasty has decreased, but not eliminated, restenosis and the subsequent need for repeat revascularization procedures (1). For this reason, drug-eluting stents that provide antiproliferative drugs to the stented vessel wall have been designed and studied for reducing in-stent restenosis.

The pioneering QuaDDS stent (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) was designed to control neointimal proliferation through prolonged high-dose delivery of the paclitaxel derivative 7-hexanoyltaxol (QP2) via acrylate polymer membranes mounted on a novel stent design (QueST).This technology differs markedly from subsequent paclitaxel-eluting stents that use drug or drug-polymer coatings to deliver low-dose paclitaxel to inhibit restenosis (2–5).

We report final one-year outcomes from the Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial.

METHODS

Study design. The open-label, randomized, multicenter SCORE trial compared safety and performance of the QuaDDS stent versus the QueST, or other, bare metal stents in focal, de novo coronary lesions. Ethics Review

From *Herzzentrum, Siegburg, Germany; †Cardiovascular Research Foundation, New York, New York; ‡Krandkenhaus Barmherzige Brueder, Trier, Germany; §San Raffaele Hospital, Milan, Italy; ‖University Campus Biomedico of Rome, Rome, Italy; ¶Columbus Hospital, Milan, Italy; #Cardiology Clinic, Munich, Germany; **Praxisklinik Kardiologie Angiologie Radiologie, Dresden, Germany; ††Main-Taunus Heart Institute, Bad Soden, Germany; ‡‡Clinique Pasteur, Toulouse, France; §§Universita degli Studi Policlinico S. Orsola Istituto di Cardiologia, Bologna, Italy; ‖‖Center for Cardiology and Vascular Intervention, Hamburg, Germany; ¶¶Clinique du boise de Verriers, Antony, France; ##Universitatsklinikum der RWTH Aachen, Aachen, Germany; ***Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy; †††Prince of Wales Hospital, New South Wales, Australia; and ‡‡‡Boston Scientific Corporation, Natick, Massachusetts. Dr. Russell is an employee and stockholder of Boston Scientific Corp. Dr. Guagliumi consults for Boston Scientific Corp. The Cardiovascular Research Foundation (Dr. Lansky) receives educational grants from Boston Scientific Corp. The SCORE trial was initiated and sponsored by Quanam Medical Corp. (Santa Clara, California) in February 2000. Boston Scientific Corp. acquired Quanam in February 2001 and assumed responsibility for new trial management.

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Abbreviations and Acronyms

IVUS = intravascular ultrasound
MACE = major adverse cardiac event
MI = myocardial infarction
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVR = target vessel revascularization

Committees of participating institutions approved the protocol, and patients provided written informed consent before enrollment.

Enrollment, planned for 400 patients in 19 international sites, began in February 2000. In April 2001, enrollment was terminated prematurely (266 patients, 15 sites, 4 countries) because of unexpectedly high rates of adverse cardiac events (stent thrombosis cardiac death, and myocardial infarction [MI]).

Patient selection. Eligible patients (51 to 79 years of age) had documented de novo lesions in native coronary arteries, objective evidence of ischemia (stable/unstable angina, positive functional study), and clinical, hemodynamic, and angiographic indications for percutaneous transluminal coronary angioplasty. Key angiographic inclusion criteria were lesion length suitable for a single 13- or 17-mm stent with stenosis >50% and location in a native coronary vessel ≥3.0 mm and ≤3.5 mm in diameter.

Key exclusion criteria included excessive tortuosity, involvement of side branch >2.0 mm in diameter, moderate or severe calcification of the target lesion or adjacent vessel, acute MI <1 week before the procedure, stroke or transient ischemic attack <6 months before the procedure, and allergy or contraindication to aspirin, clopidogrel, ticlopidine, heparin, or stainless steel.

End points. Clinical end points included stent thrombosis rate and major adverse cardiac event (MACE), defined as cardiac death, Q-wave and non–Q-wave MI, and revascularization of the target lesion (coronary artery bypass graft or percutaneous coronary intervention). An independent Clinical Events Committee adjudicated MACE. The primary end point six months post procedure was the target vessel revascularization (TVR) rate; secondary end points were MACE, quantitative coronary angiography (QCA), and intravascular ultrasound (IVUS) assessments of restenosis. Successful reduction was predefined as a restenosis rate <20%.

Device. Control devices included commercially available uncoated stents and balloon-expandable (13- or 17-mm long; 3.0- or 3.5-mm diameter) QueST stents made of 316L surgical-grade stainless steel in a slotted tube design and mounted on an over-the-wire balloon catheter delivery system. The test stent (QuaDDS) was the QueST stent mounted with polymer sleeves with 800 μg 7-hexanoyltaxol each (Fig. 1). The 13-mm stent contained 4 sleeves (3.2 mg); the 17-mm had 5 sleeves (4.0 mg).

Procedures. Patients, randomized to QuaDDS or control stents, received a loading dose of ticlopidine (500 mg) or clopidogrel (150 to 300 mg) ≤24 h before the procedure and heparin to maintain an active clotting time of ≥250 s. Post procedure, the protocol mandated aspirin (100 mg daily) indefinitely. Ticlopidine (250 mg twice a day) or clopidogrel (75 mg every day) treatment, initially mandated for either one month (control) or six months (QuaDDS), was amended to one year for the QuaDDS stent.

Follow-up. Clinical follow-up was conducted at 1, 6, and 12 months post procedure. Coronary angiography was performed before and immediately after the index procedure and at six-month follow-up or when a patient presented with cardiac symptoms. An independent core laboratory (Cardiovascular Research Foundation, New York, New York) following established methodology performed QCA analyses. In-stent restenosis assessments included percent diameter stenosis, minimum lumen diameter, reference vessel diameter, acute gain, late loss, and restenosis rate (percent with >50% diameter stenosis). Intravascular ultrasound assessment was performed on 122 patients (66 QuaDDS; 56 control) immediately post procedure and again at six months (6).

Statistical analysis. Final data management and statistical analyses were performed by PAREXCEL International Ltd. (Waltham, Massachusetts). The primary study hypothesis was that the QuaDDS stent would reduce in-stent restenosis rates compared with bare metal stents (7,8). Statistical analyses, performed using SAS version 6.12 (SAS Institute, Cary, North Carolina), were based upon actual stent received to assess the safety performance of the stent. Continuous variables are summarized as mean ± SD and compared between treatment groups using a two-sample t test. Categorical variables are expressed as percentages and compared using two-sided Fisher's exact test. Survival analyses for freedom from MACE and target lesion revascularization (TLR) were performed using the Kaplan-Meier product-limit method and compared using the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS

The SCORE trial was terminated prematurely (266 patients) in April 2001 owing to a high rate of adverse cardiac

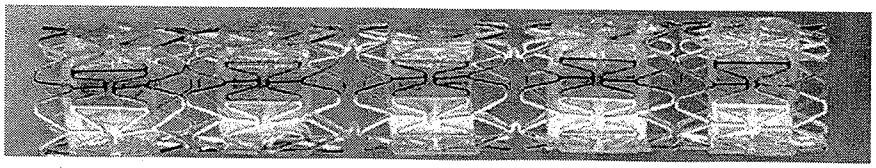

Figure 1. Photograph of the QuaDDS stent with five polymer sleeves.

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Table 1. Baseline Demographics and Clinical Characteristics

Characteristic*	QuaDDS (n = 126)	Control (n = 140†)
Gender, male (%)	81	78
Age, yrs (min, max)‡	61 (33, 79)	63 (34, 80)
Diabetes (%)	20	21
Hypertension (%)	68	64
Previous myocardial infarction (%)	39	41
Hypercholesterolemia (%)	72	78
Current smoking (%)	16	18

*No statistically significant differences between groups ($p < 0.05$). †QueST: 111; commercial uncoated: 29. ‡In accordance with the protocol, eligible patients were between 50 and 80 years old but five patients under 50 were enrolled.

events as recommended by the Clinical Oversight Committee. Long-term results were collected for 91% (244 of 266) and 76% (201 of 266) of patients at six-month clinical and angiographic follow-up, respectively, and for 88% (235 of 266) at 12-month clinical follow-up. The Clinical Oversight Committee also recommended that the SCORE trial patients be maintained on clopidogrel and followed in a long-term registry.

Baseline and procedural characteristics. Groups showed no significant differences with respect to baseline demographics and clinical characteristics (Table 1). Mean lesion lengths (QCA) were comparable (11.7 ± 4.4 mm [QuaDDS]; 12.0 ± 4.4 mm). Stent placement with post-procedure percent diameter stenosis <20% was comparable (99.7% [QuaDDS]; 99.8%).

Clinical outcomes. In the QuaDDS group, stent thrombosis rates were higher at 1, 6, and 12 months and were associated with increased rates of cardiac death and MI (Table 2). The risk for cardiac death or MI in QuaDDS patients who had a stent thrombosis was 84.6%, significantly higher than for those who did not ($p < 0.001$). Among QuaDDS patients with a stent thrombosis, 23.1% (3 of 13) had associated death, 76.9% (10 of 13) had associated MI, and 15.4% (2 of 13) had associated cardiac death and MI.

One-month overall MACE rates were higher in the QuaDDS group, attributable in part to an increase in MI, most likely related to polymer sleeve side branch occlusion.

The six-month primary end point was not met. Group MACE rates were comparable as a result of similar TVR rates (Table 2). However, the QuaDDS group showed higher rates of overall MI and non–Q-wave MI.

Twelve-month MACE rates were similar but the QuaDDS group showed higher rates of MI and cardiac death. The groups had similar survival curves for freedom from MACE and freedom from TLR (Fig. 2).

QCA and IVUS. At six-month follow-up, the restenosis rate was reduced from 32.7% (control) to 7.4% (QuaDDS [$p < 0.0001$]) (Table 3). The QuaDDS group minimum lumen diameter was larger; percent diameter stenosis and late loss were lower (Table 3).

The IVUS outcomes showing a 68% reduction in neointimal growth and a 28% increase in minimum lumen area in the QuaDDS group versus control patients were published previously (6).

DISCUSSION

The pioneering QuaDDS stent's unacceptable safety profile and failure to impact revascularization have halted further development of this high-dose, acrylate polymer sleeve delivery system. The safety outcomes from this mode of paclitaxel delivery stand in stark contrast to acceptable results obtained with other paclitaxel-eluting coated stents (2–5,9). Factors that may have contributed to the increased stent thrombosis, non–Q-wave MIs, and death are outlined in the following discussion.

Drug. Drug doses loaded on the QuaDDS stent were >10-fold above the TAXUS paclitaxel-eluting stents (e.g., 17-mm QuaDDS stent, 4,000 μg; 16-mm TAXUS stent, 108 μg) (2). Second, release was protracted for QuaDDS, with most (80%) 7-hexanoyltaxol release occurring within 90 days and continuing to six months (Quanam/Boston Scientific preclinical data on file). This contrasts with burst release of the paclitaxel within the first 48 h for the other paclitaxel-eluting stents. Hence, higher drug doses for a longer time may have delayed healing and prevented surface passivation, contributing to the QuaDDS stent's higher stent thrombosis rate.

Polymer. Long-term (90- and 180-day) porcine studies conducted subsequent to SCORE enrollment demonstrated

Table 2. 1-, 6-, and 12-Month Cumulative MACE and Stent Thrombosis

Event	1 Month			6 Months			12 Months		
	QuaDDS (n = 126)	Control* (n = 140)	p†	QuaDDS (n = 126)	Control* (n = 140)	p†	QuaDDS (n = 126)	Control* (n = 140)	p†
MACE	16 (12.7%)	4 (2.9%)	0.004	26 (20.6%)	20 (14.3%)	0.196	37 (29.4%)	35 (25.0%)	0.490
Cardiac death	2 (1.6%)	0 (0.0%)	0.223	3 (2.4%)	0 (0.0%)	0.105	5 (4.0%)	0 (0.0%)	0.023
MI	15 (11.9%)	3 (2.1%)	0.002	20 (15.9%)	3 (2.1%)	< 0.001	24 (19.0%)	3 (2.1%)	< 0.001
Q-wave MI	1 (0.8%)	0 (0.0%)	0.474	3 (2.4%)	0 (0.0%)	0.105	6 (4.8%)	0 (0.0%)	0.011
Non–Q-wave MI	13 (10.3%)	3 (2.1%)	0.008	15 (11.9%)	3 (2.1%)	0.002	16 (12.7%)	3 (2.1%)	0.001
Target vessel revascularization	3 (2.4%)	1 (0.7%)	0.348	15 (11.9%)	18 (12.9%)	0.854	25 (19.8%)	33 (23.6%)	0.552
Target lesion revascularization	3 (2.4%)	1 (0.7%)	0.348	10 (7.9%)	14 (10.0%)	0.670	18 (14.3%)	26 (18.6%)	0.410
Stent thrombosis	4 (3.2%)	0 (0.0%)	0.049	9 (7.1%)	1 (0.7%)	0.007	13 (10.3%)	1 (0.7%)	< 0.001

*Included two patients randomized to the QuaDDS stent who erroneously received a control stent. †Two-sided Fisher's exact tests; $p < 0.05$ = statistically significant. MACE = major adverse cardiac events; MI = myocardial infarction.

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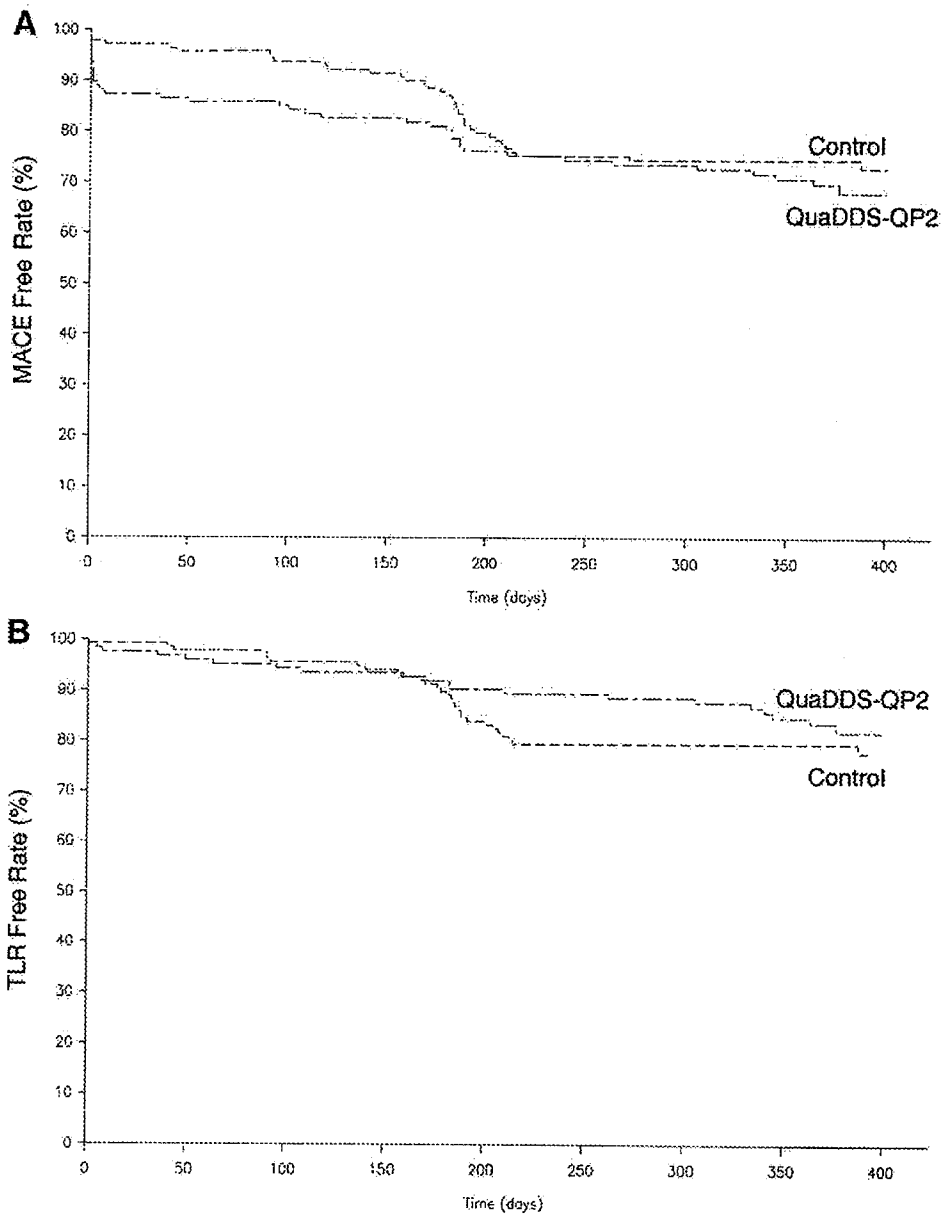

Figure 2. Freedom from **(A)** major adverse cardiac event (MACE) and **(B)** target lesion revascularization (TLR) post-procedure.

an intense inflammatory reaction with frequent granulomas and fibrosis with severe narrowing and occlusion in vessels stented with the QuaDDS stent or polymer-only sleeves (Boston Scientific data on file), indicative of vascular incompatibility of the polymer sleeves alone and with 7-hexanoyltaxol. These proinflammatory findings in the porcine model with the acrylate polymer may suggest additional mechanisms contributing to the poor QuaDDS safety profile in humans.

Sleeves. Multiple, relatively thick sleeves could potentially block side branches, leading to higher rates of periprocedural non–Q-wave MI. In contrast, paclitaxel-eluting stents using strut-conforming drug coatings have established safe clinical trial profiles (2,3,5,9).

CONCLUSIONS

Despite the limitations of open-label design, the SCORE trial outcomes demonstrate that for the QuaDDS stent, the potential anti-restenotic benefit seen with reduced binary restenosis rates is outweighed by an unacceptable safety profile. Incomplete healing suggested by ongoing stent

Table 3. Baseline, Post-Procedure, and Six-Month Angiographic Outcomes in the SCORE Trial

	QuaDDS* (n)	Control* (n)	p†
Baseline‡			
Reference vessel diameter (mm)	2.91 ± 0.43 (116)	3.00 ± 0.48 (132)	0.12
Lesion length (mm)	11.69 ± 4.38 (113)	11.98 ± 4.35 (130)	0.60
Minimum lumen diameter (mm)	0.92 ± 0.38 (116)	0.92 ± 0.46 (133)	0.99
Percent diameter stenosis (%)	68.67 ± 12.17 (116)	69.86 ± 12.95 (132)	0.46
Post-procedure‡			
Reference vessel diameter (mm)	2.97 ± 0.38 (114)	3.06 ± 0.44 (132)	0.11
Minimum lumen diameter (mm)	2.78 ± 0.37 (116)	2.91 ± 0.46 (133)	0.01
Percent diameter stenosis (%)	6.28 ± 10.25 (114)	4.43 ± 10.50 (132)	0.16
Six months‡			
Minimum lumen diameter (mm)	2.43 ± 0.54 (94)	1.79 ± 0.76 (107)	< 0.0001
Percent diameter stenosis (%)	16.4 ± 18.1 (94)	39.5 ± 23.9 (107)	< 0.0001
Binary (>50%) restenosis rate (%)§	7.4% (94)	32.7% (107)	< 0.0001
Late lumen loss (mm)	0.34 ± 0.58 (94)	1.08 ± 0.79 (107)	< 0.0001

*Mean ± SD or %. †Continuous data: two-sample *t* test; binary data: two-sided Fisher's exact test; $p < 0.05$ = statistically significant. ‡Angiographic analyses were carried out on the randomized groups. §>50% in-stent diameter stenosis, excluding patients with thrombosis.

SCORE = Study to COmpare REstenosis Rate between Quest and QuaDDS-QP2.

thrombosis and associated MACE argue that the goal for paclitaxel delivery is transient and low-level paclitaxel release as opposed to the QuaDDS design with protracted and high-dose release of 7-hexanoyltaxol.

Acknowledgments

The authors thank Laurie LaRusso, MS, ELS (Boston Scientific Corp.) for help with the manuscript and Martha Reitman, MD (Reitman Corp.) for project management.

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APPENDIX

An independent Clinical Events Committee whose members were Stephen G. Ellis, MD, Patrick L. Whitlow, MD, and E. Murat Tuzcu, MD, of the Cleveland Clinic Foundation, adjudicated MACE.

The Clinical Oversight Committee, consisting of Mary E. Russell, MD, David O. Williams, MD, and Simon Stertzer, MD, recommended that the SCORE trial be prematurely terminated owing to a high rate of adverse cardiac events.

High-dose 7-hexanoyltaxol-eluting stent with polymer sleeves for coronary revascularization: One-year results from the SCORE randomized trial

Eberhard Grube, Alexandra Lansky, Karl Eugen Hauptmann, Carlo Di Mario, Germano Di Sciascio, Antonio Colombo, Sigmund Silber, Juergen Stumpf, Nicolaus Reifart, Jean Fajadet, Antonio Marzocchi, Joachim Schofer, Pierre Dumas, Rainer Hoffmann, Giulio Guagliumi, Mark Pitney, and Mary E. Russell

J. Am. Coll. Cardiol. 2004;44;1368-1372
doi:10.1016/j.jacc.2004.06.054

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BRILLIANT-EU: Batimastat (BB94) Antirestenosis Trial Using the *BiodivYsio* Local Drug Delivery PC-Stent

Disclosures

Luis Gruberg, MD, FACC

Presenter: Ivan De Scheerder, MD, University Hospital (Leuven, Belgium)

When smooth muscle cells are activated, they secrete matrix metalloproteinases (MMP) that digest the extracellular matrix and allow cells to migrate. Batimastat and all MMP inhibitors will block MMP activity, which stops smooth muscle cell proliferation, one of the principal components of in-stent restenosis.

Batimastat is a broad-spectrum MMP inhibitor that selectively targets migrating cells. It is not cytotoxic, does not destroy healthy cells, and it prevents MMP activity, thereby preventing matrix digestion and cell migration and inhibiting smooth muscle cell migration without interfering with the re-endothelialization process. The *BiodivYsio*-batimastat stent (Biocompatibles International and British Biotech) has a smooth batimastat-PC coating and a thromboresistant surface that directly delivers the drug to the surface of the vessel. The PC coating controls the drug release, with appropriate timing of delivery, such that batimastat is delivered over a prolonged period of time.

Methods

Batimastat (BB-94) antiRestenosis trIaL utiLizing the *BiodivYsio* local drug delivery PC stent (BRILLIANT)-EU[1] was a multicenter, prospective, nonrandomized study designed to evaluate the safety and efficacy of the *BiodivYsio* batimastat stent (0.2 mcg/mm^2 of stent surface area) in 150 patients with single de novo coronary artery lesions.

Data obtained from patients enrolled in the *BioDivYsio* STent IN randomized Control Trial (DISTINCT) were used as the control data in the present study. Patients were on dual antiplatelet therapy before the procedure and were continued on therapy for an additional 1 month following the procedure.

The primary endpoint of the study was a composite of major adverse cardiac events (MACE) (death/recurrent myocardial infarction (MI)/target lesion revascularization) at 30 days. Secondary endpoints included binary restenosis, subacute thrombosis at 30-day follow-up, MACE at 6 and 12 months, and quantitative coronary angiography (QCA) at 6 months.

Baseline clinical characteristics between the 2 groups were similar (Table 1).

Table 1. Baseline Clinical Characteristics

Characteristic	Batimastat (n = 150)	Control (DISTINCT) (n = 180)
Age (yrs)	61	60
Male gender (%)	77	71
Diabetes (%)	13	21
Current smoker (%)	32	25
Hypertension (%)	46	53

Hyperlipidemia (%)	62	61
Prior stroke (%)	6	4
Prior MI (%)	34	37
Previous PCI (%)	13	18
Multiple-vessel disease (%)	31	40
Peripheral vascular disease (%)	11	6
Family history (%)	43	60
Target Vessel		
LAD (%)	36	47
LCX (%)	18	22
RCA (%)	46	30
Lesion length (mm)	11	15

LAD, left anterior descending; LCx, left circumflex, MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery

Investigators reported that 2 patients had a non Q-wave MI and 1 patient died at short-term (30-day) clinical follow-up. At long-term follow-up, there was no difference in the rate of MACE between the treatment and control groups (Table 2).

Table 2. MACE at Long-term Clinical Follow-up

Event	BRILLIANT	Control (DISTINCT)
Cardiac death	1	1
Q-wave MI	0	1
Non-Q-wave MI	3	1
Target lesion revascularization	15	11
Coronary bypass surgery	1	3
MACE	20	17

MACE, major adverse cardiac event; MI, myocardial infarction

QCA analysis data showed similar correlation of results between the patients of both studies, with no difference in minimal lumen diameter or percent diameter stenosis in the batimastat group (Figure 1).

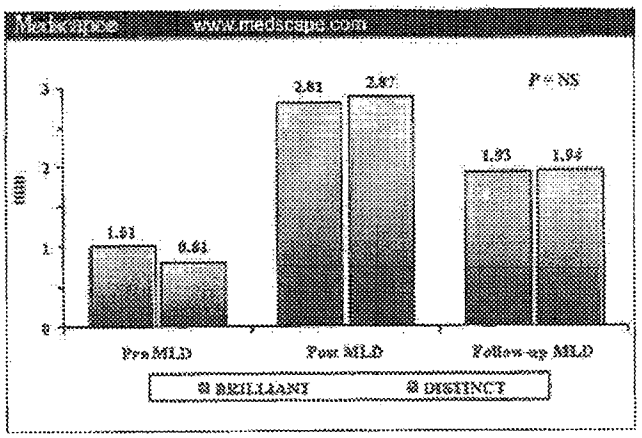

Figure 1. QCA: minimal lumen diameter.

Late loss rates were also similar for the 2 groups (0.86 vs 0.94, *P* = NS), and there was also no difference in the rate of binary restenosis (angiographic and clinical) between the group (Figure 2).

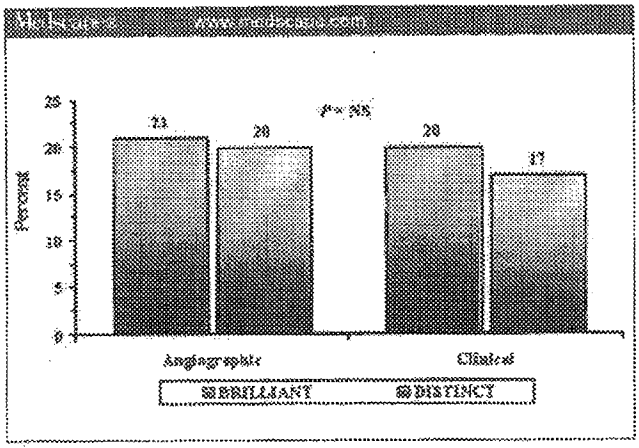

Figure 2. Restenosis rates.

Conclusions

According to the investigators, the present study suggests that the *BiodivYsio-batimastat* stent is safe for use in certain patients; however, the treated stent yields no beneficial effect on the rate of in-stent restenosis. In addition, the *BiodivYsio-batimastat* stent shows no superiority in the prevention of restenosis compared with the non-drug-eluting PC-coated *BiodivYsio* stent.

Comments

Once more, we have been fooled by a brilliant concept for the prevention of restenosis, only to realize that the real-world situation is different from the theory at hand. The present study showed that the batimastat-eluting stent is no different from the PC-coated stent, at least at the current dose

(0.2 mcg/mm^2 of stent surface area).

Reference

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Inter Partes Reexamination No. 95/001,095
Declaration of Campbell Rogers, M.D.
Exhibit 26

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From Medscape Cardiology

ENDEAVOR I: Safety and Efficacy of the ABT-578-Coated Endeavor Stent -- 12-Month Follow-up

Luis Gruberg, MD, FACC

Published: 07/07/2004; Updated: 07/12/2004

Presenter: Ian T. Meredith, MD, Monash Medical Centre (Melbourne, Australia)

The *Endeavor* (Medtronic, Minneapolis, Minnesota) drug-eluting stent is made of cobalt alloy and is coated with a phosphorylcholine coating (PC) technology that has the capability to deliver ABT-578, a rapamycin analog that inhibits cellular proliferation, thereby preventing restenosis.

ENDEAVOR I is a 100-patient, prospective, multicenter study designed to evaluate the safety and efficacy of the *Endeavor* stent in patients with *de novo*, simple, native coronary artery lesions (type A-B2, 3.0-3.5 mm reference vessel diameter, < 15 mm lesion length).

Primary Endpoint

- Major adverse cardiac events (MACE) at 30 days and late loss at 4 months by quantitative coronary angiography.

Safety Endpoint

- Target vessel failure (TVF) and target lesion revascularization (TLR) at 12 months.
- Late loss at 12 months by intravascular ultrasound at 4 and 12 months.

Results

Baseline characteristics of patients enrolled in ENDEAVOR are shown in Table 1.

Table 1. ENDEAVOR I: Baseline Clinical Characteristics

Characteristic	Patients (N = 100)
Age (yrs)	59
Male (%)	79
Diabetes (%)	16
Unstable angina (%)	39
Hyperlipidemia (%)	92
Smoker (%)	34
S/P MI (%)	47

MI = myocardial infarction; S/P = status post

The results at 30 days remained consistent throughout 4- and 12-month follow-up, with no clinical events reported beyond the first 4 months of follow-up. There were no reported deaths at any time during the follow-up period; 1% of

patients experienced myocardial infarction (MI), all of which were non-Q wave; and TVF was reported in 2% of patients at 4 months and remained unchanged at 12 months (Table 2).

Table 2. ENDEAVOR I: Hierarchical MACE

N = 100	30 Days	4 Months	12 Months
Death	0	0	0
MI (%)	1	1	1
Q wave	0	0	0
Non-Q wave	1	1	1
TLR (%)	0	1	1
TVR (%)	0	0	0
TVF (%)	0	2	2
MACE (%)	1	2	2

MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization

In-stent and in-segment late loss increased from 4- to 12-month follow-up (Figure), but there was no edge effect or late stent malapposition. At 12 months, binary restenosis was 3.3% and percent volume obstruction was 9.7%.

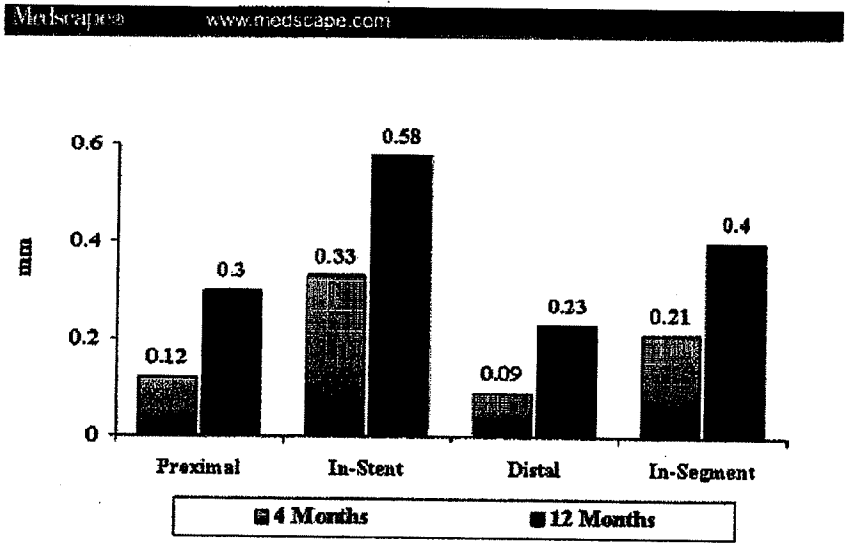

Figure. ENDEAVOR I: late loss at 4- and 12-month follow-up.

Conclusions

On the basis of the ENDEAVOR I study, investigators concluded:

1. The *Endeavor* stent is a safe device that is associated with low MACE rates at 12 months.

2. There were no cases of late thrombosis.
3. This stent was effective, with only mild in-stent and in-segment restenosis rates and no edge effect.
4. The results provide a strong platform for further clinical trials in more complex lesion subsets.

Comment

This preliminary study in a small number of patients with very simple lesions (reference vessel diameter 3-3.5 mm and lesion length < 15 mm) provided satisfactory clinical results. Due to the in-stent late loss observed, it will be crucial to follow the outcome of patients with more complex lesions treated with the *Endeavor* stent in other studies making up the ENDEAVOR stent program. However, at this point in time, it may be too early to speculate on the clinical implications of the increased late loss.

Authors and Disclosures

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Disclosure: Dr. Gruberg has no significant financial interests or relationships to disclose.

2:30 p.m.

823-3 **Oral Sirolimus for Recalcitrant In-Stent Restenosis**

Paul S. Teirstein, Jeffrey W. Moses, Mindy R. Fernandez, Prabhtej Brara, Mark A. Grise, Mehran Moussavian, John P. Reilly, Martin B. Leon, *Scripps Clinic, La Jolla, California, Lenox Hill Hospital, New York, New York.*

Background: Catheter-based radiation is an FDA approved treatment for in-stent restenosis, but not all patients are candidates for brachytherapy. Sirolimus-eluting stents are an effective therapy for restenosis, but this new device is currently not available to most patients in the United States. Oral sirolimus, however, is FDA-approved to prevent rejection after renal transplantation. We have offered oral sirolimus to selected "no-option" patients who are at especially high risk for recurrent restenosis.
Methods: Patients were treated with a sirolimus loading dose of 6 mg 4-24 hours post-PTCA, followed by 2 mg/day for 4 weeks. A one month course of therapy was selected because in the RAVEL trial, efficacy was demonstrated using stents that delivered sirolimus over a 4-6 week duration. For most patients, the cost of a 4-week drug regimen (about $400) was reimbursed by their insurance provider. Serum electrolytes, lipid profile, renal panel, and complete blood counts were measured at 1, 3, and 5 weeks after drug initiation. Patients are contacted monthly to determine adverse reactions, death, myocardial infarction, and need for repeat revascularization.
Results: To date, 11 patients at high risk for restenosis have been treated with oral sirolimus and patients are accruing at approximately 3/week. Indications included: failed radiation therapy = 7; lesion length too long for brachytherapy = 1; vessel diameter too small for brachytherapy = 3. The mean age was 57.6 +/- 11.8 and 63.6% were diabetic. The target lesion was the left anterior descending in 7 patients; right coronary in 0; and circumflex in 2; radial graft to LAD in 1; saphenous vein graft to obtuse marginal branch in 1. The mean number of previous restenoses per patient was 3.2 +/- 1.8. The mean time interval between the sirolimus treatment procedure and the immediately preceding revascularization procedure was 5.4 +/- 2.4 months. With very early follow-up, no adverse advents have occurred.
Conclusion: Patients at extremely high risk for recurrent restenosis are receiving a 30-day course of oral sirolimus. Six-month follow-up results will be presented.

2:45 p.m.

823-4 **SCORE Trial Interim Safety Results: Despite Efficacy, Late Stent Thrombosis With the QuaDDS-QP2 Stent**

Eberhard Grube, Karl Hauptmann, Antonio Colombo, Germano DiSciascio, Sigmund Silber, Roland Bach, Carlo DiMario, Nicholas Reifart, Jean Fajadet, Score Investigators, *Herzzentrum Siegburg, Siegburg, Germany.*

Background: The purpose of the SCORES trial was to compare safety and efficacy of the QuaDDS-QP2 stent with control, bare stents (QueST or any bare metal stent) for treatment of *de novo* lesions. The QuaDDS-QP2 stent has 5 polymer sleeves that contain 4000 µg of QP2, a taxane derivative intended to inhibit restenosis. QCA analysis (reported separately) showed improvements in restenosis despite including cases of stent thrombosis. The purpose of this abstract is analysis of long term clinical results reflecting high dose taxane delivery using the sleeve technology.
Methods: Of 400 planned patients at 15 sites, 266 patients were randomized and treated with either the QuaDDS-QP2 stent (N=128) or the QueST (112) or any bare metal stent (26)(Total control N=138). Enrollment was stopped due to increased early MACE events. Currently, 248 patients (120 QuaDDS; 128 QST) have completed the 6 month visit, including 18 patients that were lost to follow-up, dropped out or died. All MACE were adjudicated by a centralized Safety Adjudication Committee.
Results: The QuaDDS group had 12 stent thromboses (four at least 6 months after stent placement; ten associated with MI) and 5 deaths (three associated with stent thrombosis, one with multi-organ failure post CABG, one with cardiogenic shock).

Parameter	QuaDDS-QP2 (N=128)	QueST (N=138)	P value
Stent Thrombosis	12 (9%)	0	<0.01
Peri-procedural	1		
Discharge-Day 30	3		
Day 30-180	4		
After Day 180	4		
Death (cardiac-related)	5 (4%)	0	0.02

Conclusions: Early and late stent thromboses limit the utility of QuaDDS-QP2 stent despite its beneficial effect on restenosis. Likely explanations include high drug dose, sleeve capacity or sleeve properties.

3:00 p.m.

823-5 **Incidence of Incomplete Stent Apposition at Six Month Follow-Up in the Multi Center RAVEL Trial**

M. Degertekin, E. Regar, K. Tanabe, J. E. Sousa, A. Colombo, G. Guagliumi, J. L. Guermonprez, P. de Feyter, M. C. Morice, Patrick W. Serruys, *Thoraxcenter, Rotterdam, The Netherlands.*

Background: Patients with single de-novo lesions were randomized to receive 18 mm Sirolimus eluting stent (SES) Bx-VELOCITY™ or an uncoated stent (US) Bx- VELOCITY™ (Cordis). Most of incomplete stent appositions (ISA)seen immediately after stent deployment resolve at 6-month follow-up (FU). Since lack of intimal proliferation at 6-month has been described after SES implantation, we investigated the incidence and the clinical implication of ISA in the RAVEL study, a double-blinded controlled trial of SES versus US. **Methods:** In a subset of patients clinical, QCA and 3D IVUS FU was performed at 6-month. Based on the consensus of three independent analysts ISA was defined as ≥1 strut clearly seperated from vessel wall with evidence of blood speckles behind the strut. Percentage of neointimal hyperplasia (NIH) was calculated as neointimal volume / stent volume. Late lumen loss was defined as MLD post procedure-MLD FU. **Results:**

	SES (n=50)	US (n=49)	p-value
RD post (mm)	2.79 ± 0.48	2.84 ± 0.42	ns
RD FU (mm)	2.82 ± 0.51	2.48 ± 0.42	< 0.001
MLD post (mm)	2.47 ± 0.43	2.46 ± 0.39	ns
MLD FU (mm)	2.40 ± 0.49	1.55 ± 0.59	< 0.001
Late Loss (mm)	0.06 ± 0.29	0.90 ± 0.57	< 0.001
TLR (%)	0 (0/50)	10 (5/49)	< 0.001
Late Occlusion (%)	0 (0/50)	0 (0/49)	ns
IVUS Lum.Vol.(mm^3)	125.4 ± 33	94.1 ± 41.2	< 0.001
IVUS NIH (%)	2.21 ± 7.5	28.7 ± 21.3	< 0.001
IVUS ISA	**10 (20%)**	**2 (4%)**	**< 0.015**

There were no significant differences in QCA and IVUS measurements between patients with or without ISA.
Conclusion: The incidence of ISA in patients with SES at 6-month FU is significantly higher than with US. Since no IVUS was performed after deployment, we cannot conclude whether this incomplete apposition is the persistence of early ISA without any tissue proliferation or the development of late ISA. Although ISA was not associated with adverse clinical events, long-term FU is needed to investigate the clinical implication of this IVUS observation.

3:15 p.m.

823-6 **Paclitaxel Coating Reduces In-Stent Restenosis: A Serial Volumetric Intravascular Ultrasound Analysis**

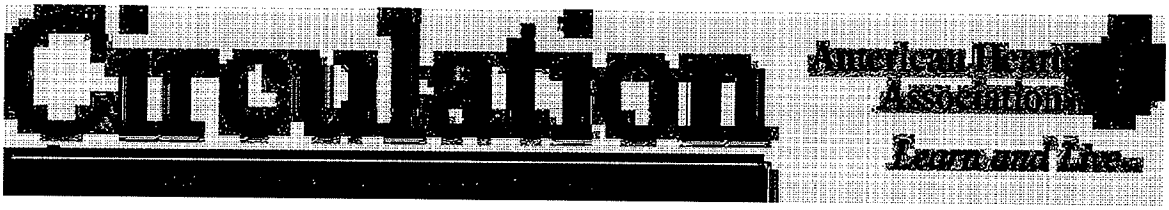
Myeong-Ki Hong, Gary S. Mintz, Seong-Wook Park, Jae-Joong Kim, Cheol Whan Lee, Neal E. Fearnot, William D. Vorhees, Neil J. Weissman, Seung-Jung Park, *Asan Medical Center, University of Ulsan, Seoul, South Korea.*

Background: In-stent restenosis (ISR) is secondary to intimal hyperplasia (IH). Paclitaxel inhibits microtubule formation rendering cells cytostatic; it inhibits restenosis in animal models. The SupraG stent is a 316L stainless-steel slotted-tube design; stents are coated with pure paclitaxel that is attached to the metallic stent without a polymer. **Methods:** ASPECT was a 3-center trial of paclitaxel-eluting stents vs placebo. 177 pts with single *de novo* or non-ISR lesions were randomized to placebo or low or high doses in a 1:1:1 ratio. If a second stent was needed, then an uncoated stent was deployed. Pts were treated with antiplatelet agents for 6 mos. The current intravascular ultrasound (IVUS) analysis was a single center substudy of ASPECT. Complete post-stent and follow-up IVUS was available in 81/102 pts: 25 control, 28 low dose, and 28 high dose. All stents were 15mm long; nominal diameters were 2.5-3.5mm. Cross-sectional analysis was performed every 1mm; volumes were calculated using Simpson's rule. **Results:** IVUS findings are shown in the Table. With increasing doses, there was a stepwise reduction in follow-up IH volume (pANOVA<0.0001). Post-hoc analysis showed a decrease in IH volume when low dose was compared to control (p=0.012) and when high dose was compared to control (p<0.0001), but not when low and high doses were compared. **Conclusions:** Taxol-eluting stents are effective in reducing in-stent neointimal tissue proliferation and in-stent restenosis in man.

Follow-up IVUS Results

	Control	Low Dose Paclitaxel	High Dose Paclitaxel
Stent volume, mm^3	104±26	104±32	101±27
Lumen volume, mm^3	72±27	85±35	89±27
IH volume, mm^3	31±22	18±15	12±14

Inter Partes Reexamination No. 95/001,102
Declaration of Campbell Rogers, M.D.
Exhibit 101



TAXUS I: Six- and Twelve-Month Results From a Randomized, Double-Blind Trial on a Slow-Release Paclitaxel-Eluting Stent for De Novo Coronary Lesions

Eberhard Grube, Sigmund Silber, Karl Eugen Hauptmann, Ralf Mueller, Lutz Buellesfeld, Ulrich Gerckens and Mary E. Russell

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